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ARTICLE

Stereoselective annulation between an allene, an alkene, and two nitrosoarenes to access bis(isoxazoliodine) derivatives

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Abstract: This work reports metal-free annulations between one allene, two nitrosoarenes and one electron-deficient alkene to afford bis(isoxazolidine) derivatives stereoselectively. This process involves an initial formation of isoxazolidin-4-imine oxides, followed by their dipolar [3+2]-cycloaddition with electron-deficient alkenes. To highlight the utility, the annulations of 5-alleneyl-1-enes with nitrosoarenes were also feasible to afford desired bis(isoxazolidine) products with excellent stereocontrol. Resulting bis(isoxazolidine) products produced from two systems were reduced with Zn/MeOH to induce reductive N-O cleavages, yielding branched polyaminols stereoselectively.

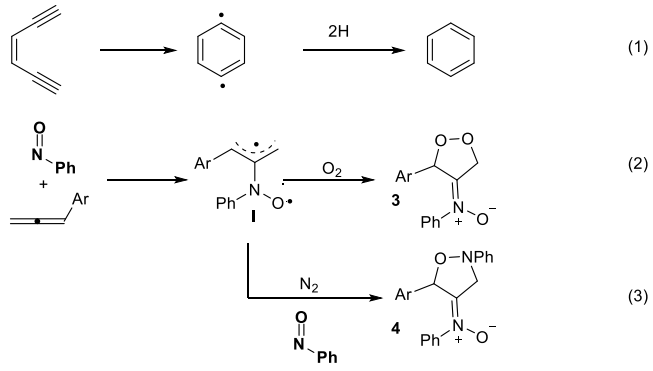
Introduction

Radical annulations via diradical intermediates are well documented in the literatures, but their utilities are poorly explored.[1] Diradical annulations typically employ hazardous diazo[2-3] and special precursors,[4] thus lacking general utility. Although commonly used π-bond motifs generate diradicals thermally, as exemplified with Bergman (eq 1) and Myers-Saito reactions, their utility is restricted to intramolecular aromatizations.[5] The formation of reactive 1,*n*-diradicals from readily available alkenes, alkynes, and allenes to enable diverse annulations is highly desirable in synthetic chemistry.

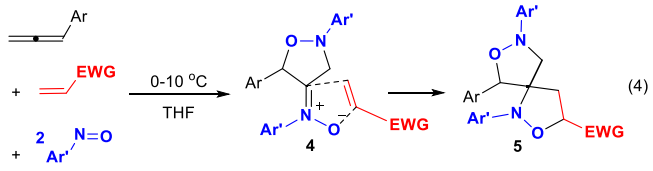
Nitrosoarenes are powerful reagents for the *N,O*-functionalizations of dienes, and alkynes via Lewis acid-catalyzed annulatios.[6-7] Theoretical calculations by Houk[8,9] suggest that the reactions of nitrosoarenes with alkenes or alkynes likely generate 1,4-diradicals**,** which cannot be synthetically utilized because of their transient nature. In the context of arylallenes, we recently reported[10] their reactions with nitrosoarenes to generate 1,4-diradical species **I** that were detectable by EPR (eq 2). Such 1,4-diradicals **I** can be trapped by ground-state O_2 to yield 1,2-dioxolanes **3** below 0 ^{o}C (eq 2); otherwise, diradicals **I** accept a second nitrosoarene to yield isoxazolidin-4-imine oxides **4** (eq 3).

To expand the utility of such 1,4-diradicals, this work[10] reports one-pot annulations between one allene, two nitrosoarenes and one olefin, yielding bis(isoxazolidine) species **5** with high stereoselectivity. This reaction sequence

Previous reports:



This work: Diradicals for four component annulations



generates isoxazolidin-4-imine oxides **4** initially, followed by their dipolar [3+2]-cycloadditions with electron-deficient alkenes. Importantly, the reductive N-O cleavage of resulting bis(isoxazolidine) species **4** provides branched polyaminols with high stereocontrol. Notably, readily available 5-allenyl-1-enes were treated with nitrosoarenes under ambient conditions to yield bis(isoxazolidine) derivatives stereoselectively, further highlighting the synthetic utility.

Many bioactive molecules comprise not only one nitroxy ring, but also amino and alcohol functionalities; selected examples **I-VI** are depicted in Figure 1.[11] A rapid synthesis of these highly *N,O*-functionalized molecules is synthetically challenging. We envisage that one-pot stereoselective construction of a bicyclic ring bearing two N-O moieties is a

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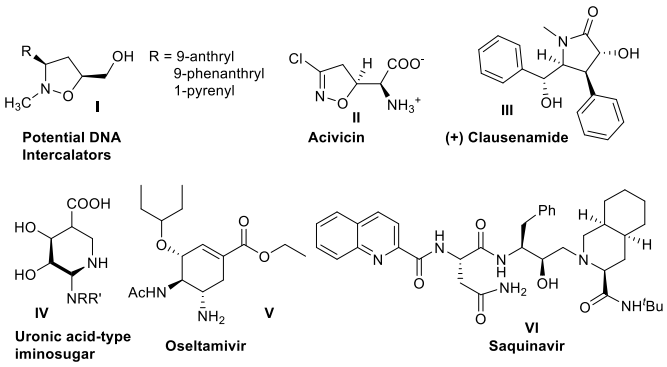
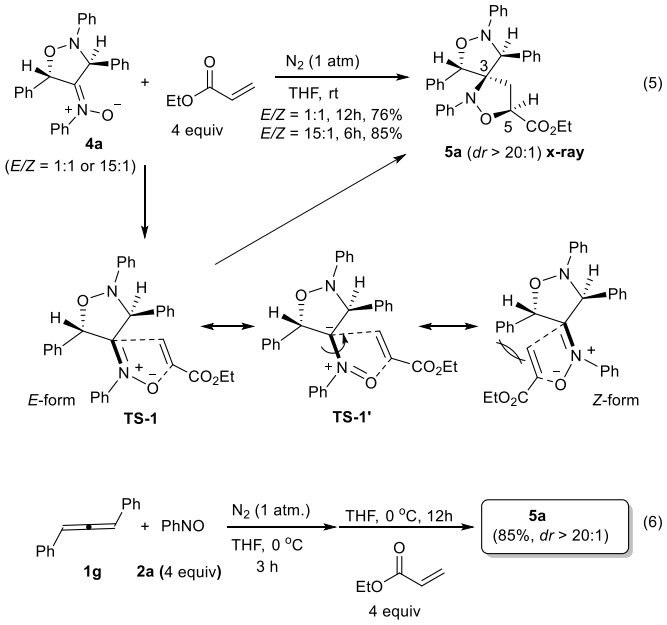


Figure 1. Representatives of several bioactive molecules

viable route. In this work, a successive N-O cleavage of two nitroxy rings of resulting bis(isoxazolidine) products **5** to afford polyaminols is also described.

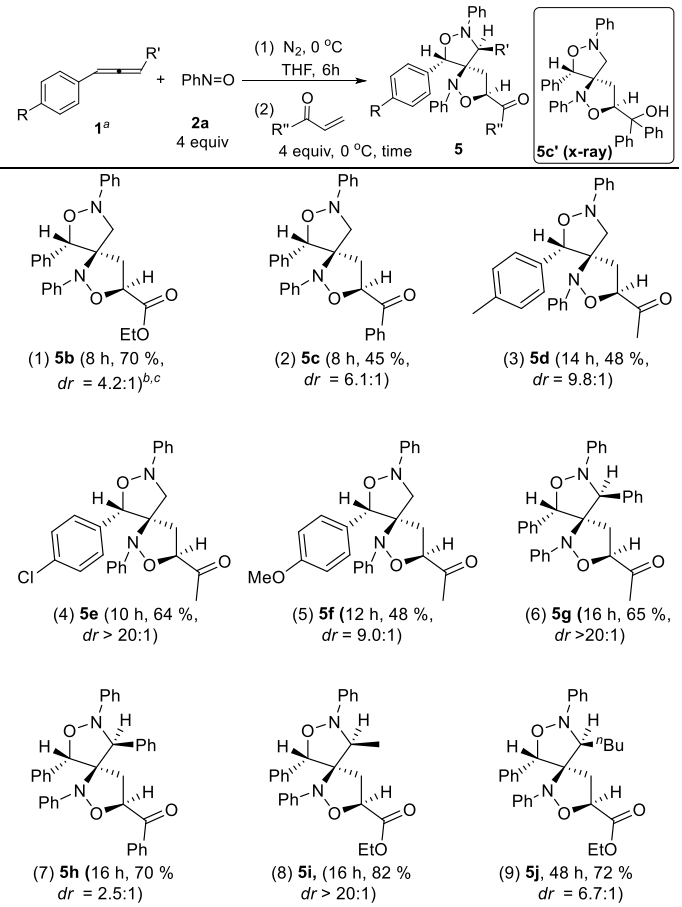
Results and Discussion

Unlike 1,2-dioxolanes **3**, the nitrone functionality of isoxazolidin-4-imine oxides **4** can undergo intermolecular [3+2]-cycloadditions with electron-deficient alkenes stereoselectively. Compound **4a** was prepared in two isomeric ratios, *E/Z* = 1/1 and *E/Z* = 15/1, respectively at 25 °C and 0 °C, according to eq 3. To exploit the alkene cycloaddition, an *E/Z* =1:1 mixture of compound **4a** was treated with ethyl acrylate to afford bis(isoxazolidine) compound **5a** as a single



diastereoisomer (*dr* > 20:1, 12 h, eq 5). This diastereoisomer was obtained efficiently also from the *E*-form of initial **4a,** but in a comparatively shorter reaction time (6 h). Accordingly, the *E*-isomer of nitrone **4a** is much more active than its *Z*-analogue, whereas the less reactive *Z*-form isomerized completely to its *E*-isomer during this cycloaddition. For the *Z*-isomer, a steric interaction between the acrylate and phenyl group decreases their cycloaddition reactivity. The molecular structure of compound **5a** was confirmed with X-ray diffraction.[12] An analysis of this X- ray structure revealed a preferable *exo*-3,5-cycloaddition of the alkene with *E*-configured **4a**; the nitrone oxygen is linked at the ***C***-CO_2Et carbon. This 3,5-regioselectivity (eq 5) typically occurs with unsubstituted enol ethers[13] and substituted electron-deficient alkenes such as ethyl *E*-but-2-enolate.[14] Unsubstituted 2-en-1-ones and 2-en-1-als preferable afford 3,4-regioisomers instead. Our 3,5-regioselectivity is rationalized with a steric effect such that a large isoxazolidine ring is preferably attacked with an alkene end to result in a 3,5-regioselectivity. The overlap between nitrone and alkene is controlled by a less hindered exo-face with the alkene lying away the phenyl group, as depicted in **TS-1** or **TS-1'**. The feasible *Z-E* isomerization of isoxazolidin-4-imine oxide **4a** indicates the contribution of an alternative resonance form, as in state **TS-1'**, in which the negative carbon terminus is stabilized with the adjacent oxygen and nitrogen atoms. Our next aim was to achieve a one-pot operation involving an initial treatment of allene **1g** with nitrosobenzene **2a** (4 equiv) in cold THF (0 °C, 3 h) to complete the consumption of allene **1a**; to this resulting

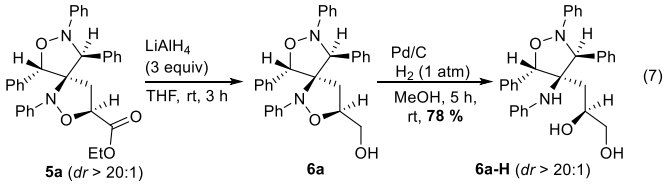
Table 1. One-pot synthesis of bicyclic isoxazolidines.



[a][1] = 0.16 M; [b]In entry 1, this ratio was obtained on heating the crude products with DBU (20 mol%) in hot THF (60 °C, 5 h); the *dr* ratio of this crude product is 44:44;6:6; [c]Product yields are reported after purification from a silica column.

solution was added ethyl acrylate (4 equiv) to complete an alkene/nitrone cycloaddition (eq. 6).

We investigated the scope of these new cascade [3+2]/[3+2]-annulations using nitrosobenzene, various allenes and electron-deficient olefins such as enones and acrylates; the results are summarized in Table 1. Styrenes failed with these reactions. Herein, resulting products **5b**-**5j** followed a stereochemical course like that of parent species **5a**. Among compounds **5a** and **5b**-**5f**, their major or single diastereomeric products have similar ^{1}H NMR patterns, indicative of the same stereochemistry. This hypothesis is confirmed by X-ray diffraction[12] of alcohol **5c'** derived from compound **5c**. For phenylallene **1a**, their N-O annulation products **4** were difficult to purify, but were trapped with unsaturated esters and ketones to afford bis(isoxazolidine) species **5b**-**5d** in satisfactory diastereoselectivity (*dr* = 4.2:1 and 6.1:1). In entry 1, crude product **5b** was obtained in four diastereomers with a ratio 44:44:6:6; these isomeric mixtures were subsequently converted to two diastereomers in a ratio 4.2:1 through a DBU-catalyzed epimerization. For 3-phenyl, methyl and *n*-butyl-substituted phenylallenes, their resulting bis(isoxazolidine) compounds **5h**-**5k** were obtained with satisfactory yields and high diastereoselectivities in most instances (entries 7-9).



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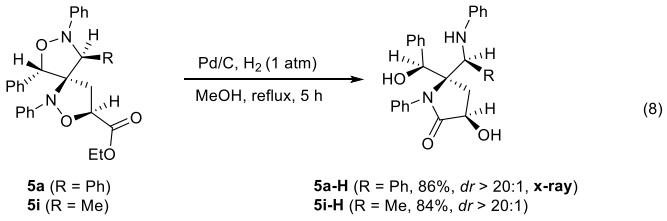
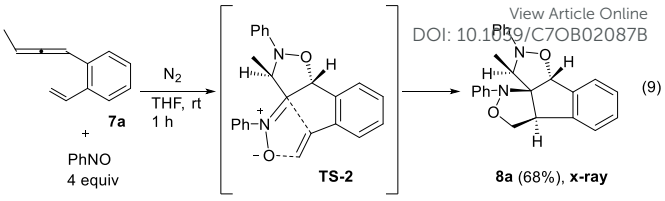


(8)

For bis(isoxazolidine) **6a,** one of the two the isoxazolidine rings was selectively cleaved with H_2. An initial treatment of this species with $LiAlH_4$ (3 equiv) afforded crude alcohol **6a** that was further reduced with Pd/C/H_2 (1 bar) in MeOH (23 °C) to yield monocyclic isoxazolidine **6a-H** as a single diastereomer (*dr* > 20:1, eq 7). In this transformation, the alcohol of **6a** is coordinated on the Pd surface to facilitate a reductive cleavage of its proximate isoxazolidine ring. To achieve a cleavage of two N-O rings, we treated compounds **5a** and **5i** with Pd/C/H_2 (1 bar)[15] in MeOH under reflux (5 h) to produce the corresponding lactams **5a-H** and **5i-H** efficiently; the molecular structure of compound **5a-H** was characterized with x-ray diffraction (eq 8).[12]

The utility of these cascade annulations is significantly expanded by their applicability to readily available 1-allenyl-5-ene **7a,**[16] which reacted well with nitrosobenzene (4 equiv) in THF (25 °C, 1 h) to afford azacyclic product **8a** as a single dia-

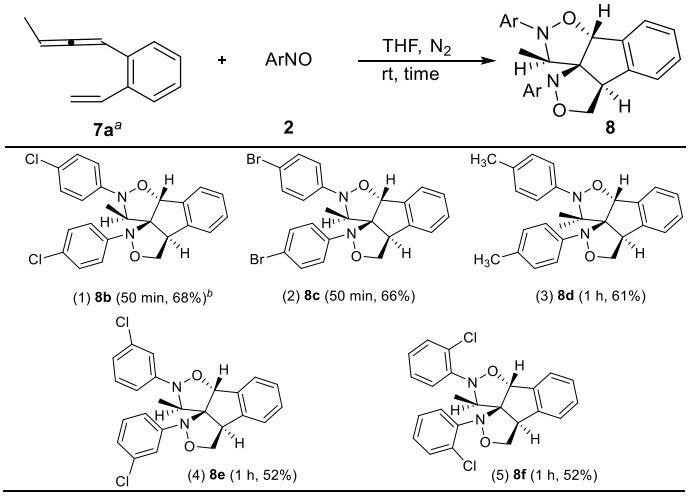


(9)

-stereomer (eq 9). The stereochemical course of these N-O annulations, as depicted in **TS-2**, is exactly the same as those (**TS-1**) in their intermolecular fashions. The molecular structures of this annulation product **8a** was elucidated by X-ray diffraction.[12]

The scope of this intramolecular four-component annulation was compatible with various nitrosoarenes (**2b**-**2f**) to yield desired bis(isoxazolidine) species **8b-8f** as single diastereomers; the results are summarized in Table 2. Herein, products **8a-8e** were obtained in 52-68% yields because their frameworks are very strained with three five-membered rings fused together. For nitrosobenzenes **2b**–**2d** bearing electron-withdrawing (-Cl, -Br) and electron donating (-CH_3) groups at

Table 2. Annulations with various nitrosoarenes.



[a][**7a**] = 0.10 M, [**2**] = 4 equiv; [b]Product yields are reported after purification from a silica column.

the *para*-phenyl positions, their reactions with 1-allenyl-5-ene **7a** yielded desired products **8b**–**8d** in 61–68 % yields (entries 1–3). Under similar conditions, *ortho* and *meta*-substituted chlorophenyl nitroso species **2e** and **2f** yielded desired bisisoxazolidines **8e** and **8f** in 52 % yields (entries 4-5).

We expanded the scope of this cascade annulation with various 1-allenyl-5-enes under optimum conditions. Table 3 (entry 1) shows the suitability of this annulation reaction for substrates **7b** bearing a *trans*-propenyl (R^4 = Me, R^3 = H), yielding desired **8g** in 67 % yield; the two *trans*-CH-CHMe protons of compound **8g** are indicated from the ^{1}H NOE experiments. Such a stereochemistry is consistent with typical alkene/nitrone cycloadditions through a concerted pathway.[17] The reaction scope was extendible to additional substrates **7c** and **7d** bearing different alkyl and aryl substituents (R^1= Me, R^3= R^4= Me; R^1= Ph, R^2= H, R^3= R^4= Me), yielding desired

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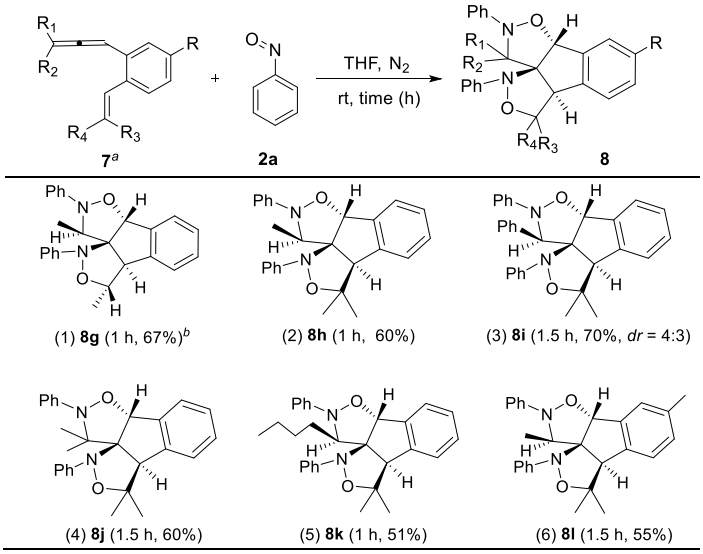
products **8h** and **8i** in 60–70 % yields (entries 2 and 3); herein, compound **8i** was present as a mixture of two diastereomers (*dr* = 4:3). The sterically hindered substrate **7e** (R^1=R^2=R^3=R^4= CH_3) was also compatible to this annulation reaction; thus giving the desired azacyclic product **8j** in good yield (60 %, entry 4). For substrate bearing long chain alkyl group **7f** (R^1= *n*-Butyl, R^2=H, R^3=R^4= CH_3); their corresponding product **8k** was obtained in 51 % yield (entry 5). To enhance the further reaction scope, we synthesized additional

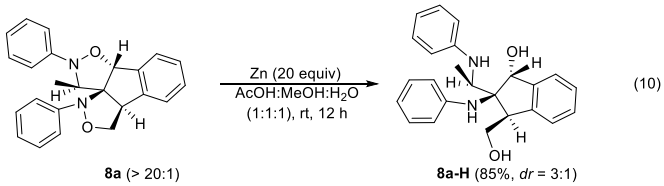
Table 3. Annulations with various 5-allenyl-1-enes.



[a][**7**] = 0.10 M, [**2**] = 4 equiv; [b]Product yields are reported after purification from a silica column.

substrate **7g** (R= Me); thus giving the desired product in 55% yield (entry 6).

Shown in eqs 10-11 are the reductive N-O cleavage of resulting bis(isoxazolidine) species **8a** and **8b** via treatment with Zn (20 equiv) in AcOH/MeOH/H_2O at room temperatures,[18] yielding highly functionalized aminoalcohols **8a-H** and **8b-H** in 85% and 87% yields respectively. Two diastereomers were obtained for compounds **8a-H** because of an epimerization at the tertiary carbon center. We only



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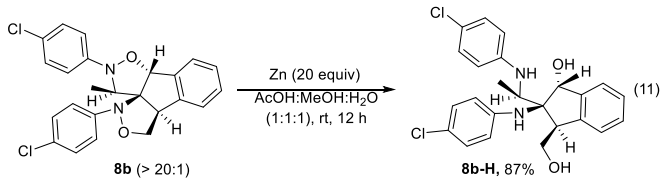

(11)

observed one diastereomeric product for compound **9b** bearing a 4-ClC_6H_4NH group.

Conclusions

Stereoselective annulations between one allene, two nitrosoarenes and one electron-deficient alkene have been developed to yield bis(isoxazolidine) derivatives with high stereoselectivities. This reaction sequence involves an initial formation of isoxazolidin-4-imine oxides, followed by their dipolar [3+2]-cycloaddition with electron-deficient alkenes. Herein, *exo*-3,5-cycloadditions between isoxazolidin-4-imine oxides **4** and alkenes control the reaction stereoselectivity. To highlight the utility, the annulations of 5-alleneyl-1-enes with two nitrosoarenes were also tested, and bis(isoxazolidine) products were produced with excellent stereocontrol. Resulting bis(isoxazolidine) species derived from two distinct systems were reduced with Zn/MeOH to induce reductive N-O cleavages, yielding branched polyaminols stereoselectively.

Experimental section

General Remarks

Unless otherwise noted, all reactions were carried out under a N_2 atmosphere in reaction tube. Tetrahydrofuran was dried with sodium and benzophenone and distilled before use. Reagents were purchased from commercial sources and used without purification, unless otherwise stated. Reactions were magnetically stirred and monitored by thin layer chromatography carried out on 0.25 mm E. Merck silica gel plate (60_f 254) using UV light as visualizing agents and/or potassium permanganate ($KMnO_4$). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 MHz, Varian 400 MHz, Varian 500 MHz, Varian 600 and Varian 700 MHz spectrometers using chloroform-*d* ($CDCl_3$) as the internal standard.

Standard procedure for synthesis of 5a:

A 10-mL flask was charged with nitrosobenzene **2a** (0.446 g, 4.17 mmol) under N_2, and added with dry THF (3 mL); the resulting solution was cooled to 0 °C. To this solution was added a dry THF solution (3.5 mL) of compound **1g** (0.2 g, 1.04 mmol) before it was stirred for 3 h. To this solution was added ethyl acrylate (0.417 g, 4.17 mmol, 4 equiv); the resulting mixture was stirred for 12 h at 0 °C. The solution was then concentrated under reduced pressure, and purified on a silica column (10% ethylacetate/hexane, R_f = 0.7 in 20% ethylacetate/hexane) to afford compound **5a** (0.44g, 0.885 mmol, 85%) as white solid.

Standard procedure for synthesis of 6a-H:

To a suspension of $LiAlH_4$ (0.023g, 0.592 mmol), in dry THF (10 mL) was added a solution of ethyl (*3S,5R,6S,9S*)-1,6,8,9-tetraphenyl-2,7-dioxa-1,8-diazaspiro-[4.4]nonane-3-arboxylate **5a** (100 mg, 0.197 mmol) in THF (2 mL) at 0 °C. After stirring at room temperature for 3 h, the reaction was quenched by the careful addition of water at 0 °C, then filtered through a celite bed, dried over anhydrous $MgSO_4$, and concentrated to afford

crude ((*3S,5R,6S,9S*)-1,6,8,9-tetraphenyl- 2,7-dioxa-1,8-diazaspiro[4.4]nonan-3-yl)methanol **6a** as colorless liquid. To a methanol (3 mL) solution of **6a** was added to a suspension of 10% Pd/C (20.0 mg) in methanol (10 mL); the mixture was stirred under H_2 (1 atm) at room temperature for 5 h. After a complete consumption of **6a**, the solution was filtered through a celite bed, concentrated, and the residues were purified by a flash silica column using 20% ethyl acetate/hexane as eluents, to give **6a-H** (0.072 g, 0.142 mmol, 78%) as pale yellow liquid.

Standard procedure for synthesis of 8a:

To a dry THF solution (1 mL) of 1-(buta-1,2-dien-1-yl)-2-vinylbenzene **7a** (0.1 g, 0.588 mmol) was added a dry THF solution (2 mL) of nitrosobenzene (0.25 g, 2.35 mmol, 4.0 equiv); the mixture was stirred at room temperature for 1 h, and evaporated under reduced pressure. The crude mixture was purified on a silica gel column (5% ethylacetate/hexane, R_f = 0.8) to afford compound **8a** (0.161 g, 0.43 mmol, 68%**)** as light brown solid.

Spectral Data of Compound 5a: ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.59 (d, *J* =7.6 Hz, 2H), 7.27 (t, *J* =6.8 Hz, 2H), 7.22 (d, *J* =6.8 Hz, 1H), 7.18-7.11 (m, 5H), 7.07-7.04 (m, 3H), 6.95 (d, *J* =8.4 Hz, 2H), 6.86 (t, *J* =7.2 Hz, 1H), 6.81 (d, *J* =8.0 Hz, 2H), 6.55 (d, *J* =7.2 Hz, 2H), 5.44 (s, 1H), 4.82 (s, 1H), 4.68 (dd, *J* =10.0, 4.0 Hz, 1H), 4.14-4.07 (m, 2H), 2.68 (dd, *J* =9.5, 4.0 Hz, 1H), 2.45-2.39 (m, 1H), 1.18 (t, *J* =7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 170.4, 148.7, 147.2, 136.7, 136.1, 129.8, 128.6, 128.6, 128.1, 128.1, 127.8, 127.8, 127.7, 125.5, 122.5, 122.1, 116.5, 82.2, 79.3, 77.1, 76.8, 61.7, 41.1, 14.0; ESI-MS calcd for $C_{32}H_{30}N_2NaO_4$ [M+Na]: 529.2103, found: 529.2105.

Spectral Data of Compound 5b: ^{1}H NMR (600 MHz, $CDCl_3$); *dr* = 4.2:1; Major isomer; δ 7.30-7.29 (m, 3H) 7.28-7.26 (m, 3H), 7.25-7.24 (m, 2H), 7.23-7.20 (m, 4H), 7.18-7.16 (m, 3H), 5.34 (s, 1H), 4.33-4.32 (m, 1H), 4.28 (d, *J* =10.8 Hz, 1H), 4.21-4.18, (m, 2H), 3.41 (d, *J* =10.8 Hz, 1H), 2.46-2.37 (m, 2H), 1.28-1.25 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$); δ 170.9, 150.0, 146.0, 136.4, 128.9, 128.8, 128.5, 128.4, 127.1, 125.7, 122.2, 122.1, 115.2, 82.0, 80.8, 74.7, 63.2, 61.6, 41.5, 14.2; Minor isomer; ^{1}H NMR (600 MHz, $CDCl_3$); δ 7.35-7.31 (m, 3H), 7.30-7.29 (m, 3H), 7.25-7.24 (m, 2H), 7.16-7.13 (m, 3H), 6.67-6.65 (m, 3H), 4.64 (s, 1H), 4.33 (d, *J* =3.8 Hz, 1H), 4.21-4.18, (m, 2H), 4.19 (d, *J* =10.8 Hz, 1H), 2.46-2.37 (m, 2H), 1.25-1.23 (m, 3H) other protons are merged; ^{13}C NMR (150 MHz, $CDCl_3$); δ 149.6, 129.0, 128.6, 128.1, 128.0, 125.4, 122.5, 121.6, 116.1, 73.7, 73.0, 72.5, 40.1 other carbons are merged or not visible; EI^+-MS calcd for $C_{26}H_{26}N_2O_4$[M+]: 430.1893, found: 430.1887.

Spectral Data of Compound 5c: ^{1}H NMR (400 MHz, $CDCl_3$); *dr* = 6.1:1; Major isomer; δ 7.83 (d, *J* =7.6 Hz, 2H), 7.56-7.51 (m, 1H), 7.43-7.34 (m, 7H), 7.29-7.19 (m, 7H), 7.12 (t, *J* =7.6 Hz, 1H), 6.97 (d, *J* =8.4 Hz, 2H), 5.44 (s, 1 H), 4.93-4.89 (m, 1H), 4.13 (d, *J* =10.8 Hz, 1H), 3.41 (d, *J* = 10.8 Hz, 1H), 2.70-2.65 (m, 1H), 2.50-2.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 195.2, 150.0, 146.4, 136.4, 134.8, 133.7, 129.1, 128.8, 128.6, 128.5, 127.3, 125.4, 122.1, 121.6, 115.2, 83.3, 81.4, 78.1, 62.8, 39.9 two aromatic carbons merges with others; Minor isomer; ^{1}H NMR (400 MHz, $CDCl_3$); δ 6.88 (t, *J* =7.2 Hz, 2H), 6.74 (d, *J* =8.0 Hz, 2H), 4.86 (t, *J* =8.0 Hz, 1H), 4.76 (s, 1H), 4.33 (d, *J* =9.6 Hz, 1H), 4.10 (d, *J* =9.6 Hz, 1H) other protons are merged; ^{13}C NMR (100 MHz, $CDCl_3$); δ 128.1, 121.3, 116.1 other carbons are merged or not clearly visible; ESI- MS calc for $C_{30}H_{26}N_2O_3Na$ (M+Na): 485.1841, found: 485.1836.

Spectral Data of Compound 5c': ^{1}H NMR (500 MHz, $CDCl_3$); δ 7.41-7.36 (m, 7H), 7.28-7.22 (m, 8H), 7.19-7.04 (m, 7H), 6.97-6.92 (m, 3H), 5.42 (s, 1H), 4.36 (t, *J* =7.5 Hz, 1H), 4.21 (d, *J* =10.5 Hz, 1H), 3.40 (d, *J* =10.5 Hz, 1H), 3.28 (bs, 1H), 2.44 (dd, *J* =13.0, 8.0 Hz, 1H), 2.10 (dd, *J* =13.0, 7.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$); δ 150.0, 145.8, 145.5, 143.4, 136.2, 128.8, 128.8, 128.3, 128.3, 128.1, 128.1, 127.4, 127.1, 126.9, 126.8, 125.3, 124.0, 122.1, 119.6, 115.2, 82.4, 80.6, 78.6, 78.1, 62.5, 40.6; ESI-MS calcd for $C_{36}H_{33}N_2O_3$ [M+H]: 541.2491, found: 541.2481.

Spectral Data of Compound 5d: ^{1}H NMR (600 MHz, $CDCl_3$); *dr* = 9.8:1; Major isomer; δ 7.31-7.22 (m, 7H), 7.17-7.15 (m, 2H), 7.13-7.10 (m, 2H), 7.01-6.96 (m, 3H), 5.35 (s, 1H), 4.20 (d, *J* =10.6 Hz, 1H), 3.97-3.95 (m, 1H), 3.45 (d, *J* =10.6 Hz, 1H), 2.53-2.49 (m, 1H), 2.43-2.40 (m, 1H), 2.33 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$); δ 209.2, 149.9, 145.6, 138.1, 133.6, 129.1, 128.8, 127.1, 124.9, 122.2, 120.7, 115.3, 81.9, 80.4, 80.1, 63.0, 40.9, 26.1, 21.2 one carbon merge with others; Minor isomer; ^{1}H NMR (600 MHz, $CDCl_3$); δ 6.83-6.80 (m, 2H), 6.62-6.60 (m, 3H), 4.58 (s, 1H), 4.41 (d, *J* =9.6 Hz, 1H) other protons are merged; ^{13}C NMR (150 MHz, $CDCl_3$); 129.7, 128.5, 128.3, 127.9, 122.5, 120.5, 116.4, 79.1, 72.4, 72.1, 39.4 other carbons merged or not visible; ESI-MS calcd for $C_{26}H_{27}N_2O_3$ [M+H]: 415.2022, found: 415.2016.

Spectral Data of Compound 5e: ^{1}H NMR (600 MHz, $CDCl_3$); δ 7.33-7.25 (m, 8H), 7.22 (d, *J* =8.3 Hz, 2H), 7.14-7.12 (m, 1H), 7.01-6.97 (m, 3H), 5.36 (s, 1H), 4.19 (d, *J* =10.6 Hz, 1H), 3.99-3.97 (m, 1H), 3.47 (d, *J* =10.6 Hz, 1H), 2.49-2.42 (m, 2H), 2.27 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$); δ 209.0, 149.6, 145.4, 135.4, 134.1, 128.9, 128.9, 128.7, 128.5, 125.0, 122.4, 120.6, 115.4, 81.2, 80.2, 79.9, 63.0, 40.8, 26.1; ESI-MS calcd for $C_{25}H_{24}ClN_2O_3$ [M+H]: 435.1475, found: 435.1477.

Spectral Data of Compound 5f: ^{1}H NMR (700 MHz, $CDCl_3$); *dr* = 9:1; Major isomer; δ 7.31-7.23 (m, 6H), 7.19-7.17 (m, 2H), 7.13-7.09 (m, 1H), 7.00-6.96 (m, 3H), 6.86-6.83 (m, 2H), 5.33 (d, *J* =2.2 Hz, 1H), 4.21 (dd, *J* =18.5, 3.5 Hz, 1H), 3.98-3.94 (m, 1H), 3.79 (d, *J* =3.7 Hz, 3H), 3.45 (dd, *J* =18.6, 3.2 Hz, 1H), 2.52-2.48 (m, 1H), 2.45-2.40 (m, 1H), 2.26 (d, *J* =3.9 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$); δ 209.1, 159.5, 149.9, 145.7, 128.8, 128.5, 128.4, 124.9, 122.2, 120.7, 115.3, 113.8, 81.8, 80.3, 80.1, 63.0, 55.2, 40.8, 26.1 one carbon is merged; Minor isomer; ^{1}H NMR (700 MHz, $CDCl_3$) δ 6.61 (d, *J* =14.0 Hz, 3H), 4.55 (d, *J* =2.4 Hz, 1H), 4.43 (dd, *J* =17.2, 3.4 Hz, 1H), 3.80 (d, *J* =4.1 Hz, 3H), 2.37-2.32 (m, 2H), 2.25 (d, *J* =3.9 Hz, 3H) other protons are merged; ^{13}C NMR (175 MHz, $CDCl_3$); δ 129.2, 128.6, 128.3, 122.6, 120.5, 116.6, 114.3, 82.1, 72.2, 39.5, 25.8 other carbons merged or not visible; ESI-MS calcd for $C_{26}H_{26}N_2O_3Na$ [M+Na]: 453.1790, found: 453.1795.

Spectral Data of Compound 5g: ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.62 (d, *J* =7.62 Hz, 2H), 7.38-7.33 (m, 2H), 7.28-7.26 (m, 2H), 7.20-7.12 (m, 7H), 7.09 (d, *J* =8.4 Hz, 2H), 7.04-7.01 (m, 2H), 6.99-6.95 (m, 1H), 6.67 (d, *J* =8.0 Hz, 2H), 5.37 (s, 1H), 4.47 (s, 1H), 4.25-4.21 (m, 1H), 2.44-2.39 (m, 1H), 2.18-2.14 (m, 1H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 206.2, 148.9, 147.2, 136.3, 136.1, 129.8, 128.7, 128.6, 128.4, 128.4, 128.2, 128.2, 127.8, 125.6, 123.3, 123.3, 117.9, 83.0, 82.0, 80.7, 80.6, 40.5, 27.5; EI-MS calcd for $C_{31}H_{28}N_2NaO_3$ [M+Na]: 499.1998, found: 499.2004.

Spectral Data of Compound 5h: ^{1}H NMR (600 MHz, $CDCl_3$); *dr* = 2.5:1; Major isomer; δ 7.73-7.71 (m, 3H), 7.62 (d, *J* =7.9 Hz, 1H), 7.44-7.36 (m, 5H), 7.28-7.26 (m, 3H), 7.23-7.20 (m, 1H), 7.13-7.02 (m, 15H), 6.94 (d, *J* =8.0 Hz, 2H), 6.86-6.84 (m, 1H), 6.67 (d, *J* =7.5 Hz, 2H), 6.54 (d, *J* =7.6 Hz, 1H), 5.54 (s, 1H), 5.20-5.18 (m, 1H), 4.61 (s, 1H), 3.00 (dd, *J* =13.4, 5.2 Hz, 1H), 2.47-2.39 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$); δ 195.2, 148.6, 147.4, 136.9, 135.6, 134.6, 133.6, 129.9, 129.4, 128.8, 128.6, 128.6, 128.5, 128.4, 128.2, 127.7, 125.1, 124.5, 122.0, 117.5, 83.0, 81.4, 79.7, 78.2, 40.2 one carbon merged; Minor isomer; ^{1}H NMR (600 MHz, $CDCl_3$); δ 5.32 (s, 1H), 4.88-4.85 (m, 1H), 4.41 (s, 1H), 2.26-2.23 (m, 1H) other protons are merged; ^{13}C NMR (150 MHz, $CDCl_3$); δ 194.6, 149.0, 147.6, 136.5, 136.2, 135.2, 133.8, 130.1, 129.2, 128.3, 128.1, 127.8, 126.1, 123.6, 122.8, 118.3, 84.0, 81.2, 80.8, 78.9, 38.9 other carbons merged or not visible; ESI-MS calcd for $C_{36}H_{30}N_2NaO_3$ [M+Na]: 561.2154, found: 561.2153.

Spectral Data of Compound 5i: ^{1}H NMR (600 MHz, $CDCl_3$); δ 7.50-7.48 (m, 2H), 7.38-7.35 (m, 4H), 7.27-7.26 (m, 2H), 7.21-7.20 (m, 3H), 7.14-7.11 (m, 2H), 6.91-6.90 (m, 2H), 5.48 (s, 1H), 4.43-4.40 (m, 1H), 4.25-4.19 (m, 2H), 3.60 (q, *J* =6.5 Hz, 1H), 2.60-2.56 (m, 1H), 2.42 (dd, *J* =9.6, 7.8 Hz, 1H), 1.37 (d, *J* =6.5Hz, 3H), 1.27 (t, *J* =7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$); δ 171.1, 148.0, 146.9, 138.1, 128.9, 128.7, 128.2, 127.9, 127.0, 124.3, 124.1, 121.2, 119.2, 81.8, 79.4, 74.8, 69.8, 61.6, 42.0, 14.1, 11.3; ESI-MS calcd for $C_{27}H_{28}N_2NaO_4$ [M+Na]: 467.1947, found: 467.1941.

Spectral Data of Compound 5j: ^{1}H NMR (400 MHz, $CDCl_3$); *dr* = 6.7:1; Major Isomer; δ 7.47-7.38 (m, 2H), 7.39-7.31 (m, 5H), 7.27-7.24 (m, 1H), 7.21-7.07 (m, 6 H), 6.90-6.88 (m, 2H), 5.50 (s, 1H), 4.64-4.57 (m, 1H), 4.23-4.18 (m, 2H), 3.63 (t, *J* =6.0 Hz, 1H), 2.60-2.44 (m, 2H), 2.22-2.10 (m, 1H), 1.73-1.65 (m, 1H), 1.47-1.43 (m, 1H), 1.28-1.22 (m, 7H), 0.81 (t, *J* =9.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 171.1, 148.8, 147.1, 137.4, 128.9, 128.7, 128.1, 127.9, 127.4, 124.2, 124.0, 121.4, 119.0, 81.2, 79.9, 75.0, 73.2, 61.5, 41.9, 29.6, 27.6, 22.9, 14.1, 13.9; Minor Isomer; ^{13}C NMR (100 MHz, $CDCl_3$); δ 6.54 (d, *J* = 8.0 Hz, 2H), 5.32 (s, 1H), 0.88 (t, *J* =7.2 Hz, 3H) other protons are merged; ^{13}C NMR (100 MHz, $CDCl_3$); δ 170.1, 147.9, 136.9, 125.6, 123.8, 122.6, 116.9, 82.2, 79.6, 73.7, 41.3, 28.4, 23.0, 14.0 other carbon are merged or not clearly visible; EI^{+}MS calcd for $C_{30}H_{34}N_2O_4$ [M^{+}]: 486.2519, found: 486.2517.

Spectral Data of Compound 5a-H: ^{1}H NMR (600 MHz, $CDCl_3$); δ 7.75 (d, *J* =7.1 Hz, 2H), 7.54-7.52 (m, 2H), 7.48-7.45 (m, 1H), 7.39 (d, *J* =6.3 Hz, 2H), 7.33-7.24 (m, 8H), 7.04 (t, *J* =7.9 Hz, 2H), 6.69 (t, *J* =7.2 Hz, 1H), 6.41 (d, *J* =8.0 Hz, 2H), 5.84 (bs, 1H), 5.24 (d, *J* =4.6 Hz, 1H), 4.75 (d, *J* =2.4 Hz, 1H), 3.34 (bs, 1H), 2.92 (bs, 1H), 2.38 (t, *J* =8.8 Hz, 1H), 2.04-1.98 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$); δ 177.6, 146.2, 139.5, 138.8, 138.3, 129.7, 129.4, 129.1, 129.0, 129.0, 128.6, 128.5, 128.0, 118.7, 114.7, 83.5, 70.1, 67.1, 63.9, 39.9 two carbon merged with others; ESI-MS calcd for $C_{30}H_{29}N_2O_3$ [M+H]: 465.2178, found: 465.2179.

Spectral Data of Compound 5i-H: ^{1}H NMR (600 MHz, $CDCl_3$); δ 7.48-7.43 (m, 5H), 7.39 (d, *J* =7.0 Hz, 2H), 7.33-7.29 (m, 3H), 7.18-7.16 (m, 2H), 6.80 (t, *J* =6.9 Hz, 1H), 6.46 (d, *J* =7.9 Hz, 2H), 5.37 (d, *J* =7.0 Hz, 1H), 4.64 (bs, 1H), 4.49-4.46 (m, 1H), 4.08 (d, *J* =6.1 Hz, 1H), 3.6 (d, *J* =9.9 Hz, 1H), 3.41 (bs, 1H), 2.31-2.27 (m, 1H), 2.04-2.00 (m, 1H), 1.20 (d, *J* =6.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$); δ 176.8, 145.1, 140.0, 138.7, 129.5, 129.4, 129.4, 128.7, 128.4, 128.1, 119.8, 114.9, 80.8, 71.6, 68.1, 54.6, 36.9, 15.4; ESI-MS calcd for $C_{25}H_{27}N_2O_3$ [M+H]: 403.2022, found: 403.2021.

Spectral Data of Compound 6a-H: ^{1}H NMR (600 MHz, $CDCl_3$); δ 7.66 (d, *J* =7.5 Hz, 2H), 7.41-7.38 (m, 2H), 7.36-7.34 (m, 3H), 7.32-7.30 (m, 3H), 7.18 (t, *J* =7.5 Hz, 2H), 6.99 (dd, *J* =8.0, 1.0 Hz, 2H), 6.95 (t, *J* =7.7 Hz, 2H), 6.92-6.89 (m, 1H), 6.32 (d, *J* =8.5 Hz, 2H), 5.51 (s, 1H), 5.24 (s, 1H), 4.02 (bs, 1H), 3.67-3.65 (m, 1H), 3.10-3.04 (m, 2H), 1.99-1.91 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$); δ 149.3, 144.8, 137.1, 136.5, 129.3, 128.9, 128.8, 128.8, 128.6, 128.4, 128.2, 121.8, 118.8, 117.1, 116.1, 86.3, 77.6, 71.5, 68.8, 66.9, 31.2 one carbon merged with others; ESI-MS calcd for $C_{30}H_{31}N_2O_3$ [M+H]: 467.2335, found: 467.2334.

Spectral Data of Compound 8a: ^{1}H NMR (600 MHz, $CDCl_3$); δ 7.53-7.51 (m, 2H), 7.38-7.35 (m, 1H), 7.33 (d, *J* =7.5 Hz, 1H), 7.30-7.27 (m, 5H), 7.24-7.22 (m, 3H), 7.13-7.10 (m, 1H), 6.94 (t, *J* =7.3 Hz, 1H), 5.74 (s, 1H), 4.42-4.39 (m, 1H), 4.31 (t, *J* =4.8 Hz, 1H), 3.93 (dd, *J* =8.3, 4.7 Hz, 1H), 3.46 (q, *J* =6.6, Hz, 1H), 1.40 (d, *J* =3.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$); δ 148.2, 147.0, 142.6, 140.3, 130.0, 128.7, 128.6, 128.4, 126.5, 125.5, 124.6, 121.6, 121.0, 117.4, 90.0, 82.9, 71.7, 71.2, 63.2, 12.6 ; ESI-MS calcd for $C_{24}H_{23}N_2O_2$ [M+H]: 371.1759, found: 371.1755.

Spectral Data of Compound 8b: ^{1}H NMR (600 MHz, $CDCl_3$); δ 7.45 (d, *J* =8.5 Hz, 2H), 7.38-7.37 (m, 1H), 7.31-7.28 (m, 2H), 7.24-7.23 (m, 5H), 7.15 (d, *J* =8.2 H, 2H), 5.67 (s, 1H), 4.38 (t, *J* =7.2 Hz, 1H), 4.28 (s, 1H), 3.90 (d, *J* =3.0 Hz, 1H), 3.36 (d, *J* =6.6 Hz, 1H), 1.34 (d, *J* =6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$); 146.6, 145.4, 142.3, 139.9, 131.0, 130.2, 128.8, 128.6, 126.7, 126.5, 124.7, 122.4, 118.6, 89.8, 83.0, 71.7, 71.4, 63.0, 12.4 one carbon merged; ESI-MS calcd for $C_{24}H_{21}Cl_2N_2O_2$[M+H]: 439.0980, found: 439.0981.

Spectral Data of Compound 8c: ^{1}H NMR (500 MHz, $CDCl_3$); δ 7.41-7.37 (m, 7H), 7.34-7.29 (m, 2H), 7.24-7.23 (m, 1H), 7.11-7.09 (m, 2H), 5.68 (s, 1H), 4.38 (t, *J* =5.0 Hz, 1H), 4.29 (t, *J* =4.5 Hz, 1H), 3.90 (dd, *J* =8.0, 4.5 Hz, 1H), 3.37 (q, *J* = 6.5 Hz, 1H), 1.35 (d, *J* =5.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$); 147.2, 145.9, 142.3, 139.8, 131.8, 131.5, 130.2, 128.6, 126.5, 124.7, 122.6, 118.9, 118.7, 114.1, 89.8, 82.9, 71.7, 71.3, 63.0, 12.4.; ESI-MS calcd for $C_{24}H_{21}Br_2N_2O_2$[M+H]: 526.9970, found: 526.9962.

Spectral Data of Compound 8d: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 (d, *J* =8.5 Hz, 2H), 7.36 (t, *J* =7.0 Hz, 1H), 7.31-7.22 (m, 3H), 7.14-7.07 (m, 6H), 5.68 (s, 1H), 4.37 (t, *J* =7.0 Hz, 1H), 4.27 (t, *J* =4.0 Hz, 1H), 3.93 (dd, *J* =8.0, 4.0 Hz, 1H), 3.41 (q, *J* = 6.5 Hz, 1H), 2.28 (s, 3H), 2.29 (s, 3H), 1.35 (d, *J* =6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$); 145.7, 144.8, 142.9, 140.5, 135.4, 131.1, 129.9, 129.3, 129.1, 128.3, 126.4, 124.6, 121.3, 117.8, 89.9, 82.9, 71.6, 71.2, 63.1, 20.9, 20.6, 12.4; ESI-MS calcd for $C_{26}H_{27}N_2O_2$[M+H]: 399.2073, found: 399.2076.

Spectral Data of Compound 8e: ^{1}H NMR (500 MHz, $CDCl_3$); δ 7.52 (t, *J* =2.0 Hz, 1H), 7.42-7.29 (m, 4H), 7.26-7.24 (m, 2H), 7.24-7.19 (m, 3H), 7.11-7.08 (m, 2H), 6.90 (dd, *J* =8.0, 1.5 Hz, 1H), 5.72 (s, 1H), 4.39 (t, *J* =7.5 Hz, 1H), 4.31 (t, *J* =4.5 Hz, 1H), 3.90 (dd, *J* =8.0, 4.5 Hz, 1H), 3.43 (q, *J* =6.5 Hz, 1H), 1.38 (d, *J* =6.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$); 149.3, 147.9, 142.3, 139.8, 134.6, 134.5, 130.3, 129.7, 129.6, 128.7, 126.6, 125.6, 124.7, 121.4, 120.9, 119.3, 116.9, 115.3, 89.8, 83.1, 71.8, 71.2, 63.1, 12.5; ESI-MS calcd for $C_{24}H_{21}Cl_2N_2O_2$[M+H]: 439.0980, found: 439.0975.

Spectral Data of Compound 8f: ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.39-7.36 (m, 3H), 7.32-7.27 (m, 4H), 7.24-7.22 (m, 1H), 7.17-7.11 (m, 1H), 7.09-6.96 (m, 3H), 5.49 (s, 1H), 4.59 (dd, *J* =8.0, 3.9 Hz, 1H), 4.50 (t, *J* =8.0 Hz, 1H), 4.27 (q, *J* =6.8 Hz, 1H), 4.09 (dd, *J* =8.0, 4.0 Hz, 1H) 1.18 (d, *J* =6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 144.7, 144.4, 143.4, 140.7, 132.6, 130.8, 130.2, 129.8, 128.3, 127.5, 127.2, 126.5, 126.1, 125.5, 125.3, 124.1, 121.6, 90.5, 84.2, 72.6, 67.8, 62.8, 11.6 one carbon merged; ESI-MS calcd for $C_{24}H_{21}Cl_2N_2O_2$[M+H]: 409.0980, found: 439.0976.

Spectral Data of Compound 8g: ^{1}H NMR (600 MHz, $CDCl_3$); δ 7.40 (d, *J* =8.3 Hz, 2H), 7.35-7.27 (m, 7H), 7.24-7.19 (m, 3H), 7.10 (t, *J* =7.3 Hz, 1H), 6.91 (t, *J* =7.3 Hz, 1H), 5.81 (s, 1H), 3.93-3.91 (m, 1H), 3.81 (d, *J* =8.2 Hz, 1H), 3.32 (q, *J* =6.4 Hz, 1H), 1.59 (d, *J* =6.0 Hz, 3H), 1.40 (d, *J* =6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$); δ 148.4, 147.8, 141.0, 140.3, 129.6, 128.7, 128.6, 126.9, 125.3, 124.2, 121.1, 120.8, 116.3, 92.8, 82.8, 80.1, 70.8, 68.4, 17.0, 12.0 one carbon merged; ESI-MS calcd for $C_{25}H_{25}N_2O_2$[M+H]: 385.1916, found: 385.1908.

Spectral Data of Compound 8h: ^{1}H NMR (600 MHz, $CDCl_3$); δ 7.57 (d, *J* =7.4 Hz, 2H), 7.40-7.20 (m, 10H), 7.14 (d, *J* =6.7 Hz, 1H), 6.87 (t, *J* =6.5 Hz, 1H), 5.95 (s,1H), 3.98 (s, 1H), 3.23 (d, *J* =4.8 Hz, 1H), 1.64 (s, 3H), 1.39 (d, *J* =4.6 Hz, 3H), 0.87 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$); δ 148.6, 147.6, 142.2, 139.4, 129.4, 128.7, 128.4, 126.3, 125.6, 125.0, 121.3, 119.6, 115.3, 91.4, 82.5, 81.5, 77.8, 71.3, 70.5, 26.6, 23.0, 12.0; ESI-MS calcd for $C_{26}H_{27}N_2O_2$[M+H]: 399.2073, found: 399.2067.

Spectral Data of Compound 8i: ^{1}H NMR (600 MHz, $CDCl_3$); *dr* = 4:3; Major isomer; δ 7.52-7.51 (m, 1H), 7.43-7.40 (m, 3H), 7.38-7.36 (m, 2H), 7.35-7.32 (m, 3H), 7.28-7.23 (m, 5H), 7.10-7.08 (m, 2H), 7.04-7.01 (m, 1H), 6.93-6.91 (m, 1H), 6.82-6.80 (m, 1H), 6.17 (s, 1H), 4.31 (s, 1H), 4.14 (s, 1H), 1.46 (s, 3H), 0.71 (s, 3H), ^{13}C NMR (150 MHz, $CDCl_3$); δ 149.1, 147.5, 142.9, 138.3, 134.4, 129.4, 129.0, 128.4, 128.3, 128.0, 126.5, 124.6, 124.1, 121.8, 119.6, 119.3, 114.8, 114.6, 92.7, 85.5, 82.5, 82.1, 78.7, 70.1, 25.8, 22.7; ^{1}H NMR (600 MHz, $CDCl_3$); Minor isomer; δ 7.52-7.51 (m, 1H), 7.43-7.40 (m, 3H), 7.38-7.36 (m, 1H), 7.35-7.32 (m, 3H), 7.28-7.23 (m, 5H), 7.20-7.18 (m, 1H), 7.07-7.04 (m, 1H), 6.94-6.93 (m, 1H), 6.85-6.84 (m, 1H), 6.65-6.62 (m, 1H), 5.63 (s, 1H), 5.12 (s, 1H), 4.13(s, 1H), 1.53 (s, 3H), 0.81 (s, 3H) other peaks merge with others; ^{13}C NMR (150 MHz, $CDCl_3$); δ 149.4, 147.1, 143.6, 133.0, 129.6, 129.2, 128.7, 128.5, 126.2, 124.8, 119.8, 115.0, 92.0, 82.4, 73.1, 68.4, 26.1, 23.2 Other peaks merged; ESI-MS calcd for $C_{31}H_{28}N_2O_2$ [M+]: 460.2151, found: 460.2148.

Spectral Data of Compound 8j: ^{1}H NMR (500 MHz, $CDCl_3$); δ 7.34-7.24 (m, 5H), 7.23-7.14 (m, 3H), 7.02-6.98 (m, 3H), 6.84 (t, *J* =8.4 Hz, 2H), 6.62 (t, *J* =6.0 Hz, 1H), 5.48 (s, 1H), 3.99 (s, 1H), 1.63 (s, 3H), 1.55 (s, 3H), 1.32 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$); 149.4, 147.4, 143.1, 140.7, 128.7, 128.1, 125.7, 123.5, 121.4, 119.4, 115.0, 114.7, 94.9, 83.5, 83.0, 72.5, 67.4, 26.4, 24.3, 22.9, 21.6 other carbons are merged; EI^+-MS calcd for $C_{27}H_{28}N_2O_2$[M+]: 412.2151, found: 412.2154.

Spectral Data of Compound 8k: ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.45 (dd, *J* =8.0, 1.0 Hz, 2H), 7.35 (dd, *J* =8.0, 2.8 Hz, 1H), 7.29-7.25 (m, 4H), 7.24-7.23 (m, 1H), 7.19 (d, *J* =7.1 Hz, 2H), 7.16-7.13 (m, 2H), 7.06-7.02 (m, 1H), 6.84-6.80 (m, 1H), 5.96 (s, 1H), 4.07 (s, 1H), 3.25 (dd, *J* =7.3, 3.8 Hz, 1H), 2.07-2.02 (m, 1H), 1.64-1.63 (m, 1H), 1.60-1.52 (m, 5H), 1.29-1.20 (m, 2H), 0.80 (t, *J* =8.0 Hz, 3H), 0.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$); 149.3, 147.9, 142.0, 139.1, 129.4, 128.8, 128.5, 128.1, 126.5, 125.2, 124.3, 121.0, 119.3, 114.7, 91.7, 83.0, 82.6, 75.5, 71.0, 29.1, 28.1, 26.2, 23.0, 22.9, 14.0; ESI-MS calcd for $C_{29}H_{33}N_2O_2$[M+H]: 441.2542, found: 441.2535.

Spectral Data of Compound 8l: ^{1}H NMR (600 MHz, $CDCl_3$); δ 7.55 (dd, *J* =7.1, 1.0 Hz, 2H), 7.28-7.26 (m, 3H), 7.24-7.22 (m, 3H), 7.16-7.14 (m, 2H), 7.12-7.10 (m, 1H), 7.06 (d, *J* =12.0 Hz, 1H), 6.85-6.82 (m, 1H), 5.88 (s, 1H), 3.91 (s, 1H), 3.19 (q, *J* = 6.0 Hz, 1H), 2.33 (s, 3H), 1.60 (s, 3H), 1.35 (d, *J* =6.0 Hz, 3H), 0.83 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$); δ 148.5, 147.6, 142.2, 138.5, 136.5, 130.4, 128.6, 128.4, 126.7, 125.7, 124.8, 121.4, 119.5, 115.2, 91.6, 82.4, 81.5, 71.2, 70.1, 26.6, 23.0, 21.3, 12.0. ESI-MS calcd for $C_{27}H_{28}N_2O_2$[M+]: 412.2151, found: 412.2156.

Spectral Data of Compound 8a-H: ^{1}H NMR (500 MHz, $CDCl_3$); *dr* = 3:1; Major isomer; δ 7.40-7.28 (m, 3H), 7.22-7.20 (m, 4H), 7.18-7.06 (m, 3H), 6.95-6.88 (m, 2H), 6.75 (d, *J* =8.0 Hz, 2H), 5.8 (s, 1H), 4.04-4.03 (m, 1H), 3.96 (t, *J* =3.5 Hz, 2H), 3.80 (t, *J* =5.0 Hz, 1H), 1.01 (d, *J* =6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$); δ 145.2, 143.2, 139.3, 129.6, 128.7, 128.2, 124.2, 123.6, 121.3, 119.8, 117.8, 116.0, 80.0, 73.1, 64.6, 55.9, 51.5, 15.3; Minor isomer; ^{1}H NMR (500 MHz, $CDCl_3$); δ 7.40-7.28 (m, 3H), 7.22-7.20 (m, 4H), 7.18-7.06 (m, 3H,), 6.82-6.77 (m, 2H), 6.45 (d, *J* =7.5 Hz, 2H), 5.63 (s, 1H), 4.50 (dd, *J* =6.5, 1H), 4.0-3.99 (m, 2H), 3.63 (q, *J* =4.0 Hz, 1H), 1.05 (d, *J* =7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$); δ 129.5, 129.4, 128.8, 124.3, 121.9, 118.4, 117.1, 82.9, 71.2, 65.0, 51.2, 13.9 other carbons are merged or not visible ESI-MS calcd for $C_{24}H_{27}N_2O_2$[M+H]: 375.2070, found: 375.2072.

Spectral Data of Compound 8b-H: ^{1}H NMR (600 MHz, $CDCl_3$); δ 7.34 (d, *J* =7.4 Hz, 1H), 7.31-7.25 (m, 2H), 7.16-7.13 (m, 3H), 7.07 (dd, *J* =6.8, 2.0 Hz, 2H), 6.98 (dd, *J* =6.7, 2.2 Hz, 2H), 6.51 (dd, *J* =6.8, 2.0 Hz, 2H), 5.75 (s, 1H), 3.96-3.89 (m, 4H), 3.60 (t, *J* =4.3 Hz, 1H), 1.0 (d, *J* =6.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$); 144.1, 143.7, 143.2, 139.2, 129.3, 129.2, 128.8, 128.3, 125.8, 125.0, 124.1, 123.6, 120.5, 117.3, 80.2, 73.1, 64.3, 54.0, 51.9, 16.2; ESI-MS calcd for $C_{24}H_{25}Cl_2N_2$[M+H]: 443.1293 found: 443.1290.

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